Bacterial Overgrowth in The Small Intestines of Liver Cirrhosis Patients

Paulus Simadibrata Kolopaking, Rino A. Gani,** Marcellus Simadibrata Kolopaking****

ABSTRACT

Small intestinal bacterial overgrowth is a condition where the proximal small intestine harbours more than 10^5 organisms/ml intestinal fluid for a long period. Bacterial overgrowth could be found in patients with certain clinical conditions, such as intestinal anatomical disorders, intestinal motility disorders, and several diseases including liver cirrhosis. It was reported that the prevalence of bacterial overgrowth in patients with liver cirrhosis was around 30%-75%. Small intestinal bacterial overgrowth could induce various clinical conditions from mild to severe cases, therefore it is important to recognize its signs and symptoms, diagnosis, and management. This article will also review the clinical management of small intestinal bacterial overgrowth in liver cirrhosis.

Key words: Bacterial overgrowth, Small intestine, Liver cirrhosis management

INTRODUCTION

Bacterial overgrowth in the small intestines is defined as all conditions in which the proximal portion of the small intestines contains over 10^5 organisms/ml intestinal fluid for prolonged periods of time.

Bacterial overgrowth in the small intestines of patients with chronic liver disease has been reported by Martini et al over 40 years ago.[1] Since then, there have been many other studies that found a high prevalence of bacterial overgrowth in patients with liver cirrhosis, with a rate greatly varying from 30-75%. Several conditions that facilitate bacterial overgrowth in patients with liver cirrhosis include intestinal dysmotility, liver dysfunction, malnutrition, reduced gastric acid, intestinal IgA deficiency, and excessive intake of alcohol.

Most patients with bacterial overgrowth present no symptom, but when they do, symptoms can take the form of chronic diarrhea, abdominal discomfort, weight loss, nausea, vomiting, gassiness, as well as signs associated with malabsorption of fat, carbohydrates, protein, vitamin B12, and other micronutrients.[2,3,4] In patients with chronic liver disease, bacterial overgrowth is associated with hepatobilliary damage similar to that in alcoholic liver disease,[5,6,7] increased endotoxin,[8] increased production of toxic bile acids such as lithocholic acid that increases the risk of cholelithiasis, and increased toxic effect from alcohol due to excessive production of acetaldehyde, which is toxic to the liver, caused by increased ethanol metabolism.

The correlation between bacterial overgrowth and spontaneous bacterial peritonitis (SBP) has been demonstrated in a study by Casafont, et al.[1] The prevalence of SBP in patients with bacterial overgrowth turned out higher (30.7%) compared to those without (9%). This result demonstrates that bacterial overgrowth may be a predisposing factor for SBP in patients with liver cirrhosis, when bacterial translocation occurs.[9,10,11,12,13,14,15,16,17]

THE NORMAL MICROFLORA OF THE SMALL INTESTINES

The normal microflora in the lumen of the small intestines of healthy humans have not been fully described, leaving room for further investigation on their effect on the structure and function of the small intestines.[18]

Permanent Normal Flora

Normal flora of the small intestines solely consists of bacteria. Even though viruses can be cultured from the intestines of healthy children, normal viruses are not

* *Department of Internal Medicine, Faculty of Medicine of The University of Indonesia/Cipto Mangunkusumo Hospital, Jakarta, Indonesia*

** *Division of Hepatology, Department of Internal Medicine, Faculty of Medicine of The University of Indonesia/Cipto Mangunkusumo Hospital, Jakarta, Indonesia*

*** *Division of Gastroenterology, Department of Internal Medicine, Faculty of Medicine of The University of Indonesia/Cipto Mangunkusumo Hospital, Jakarta, Indonesia*

believed to reside within the intestines of healthy adults.

The gaster and the small intestines normally contain a relatively small number of bacteria.[19] The gastric microflora mainly consists of positive Gram and aerobic bacteria, with a concentration of less than 10^3 colony forming units/ml (particularly *Streptococcus*, *Staphylococcus*, *Lactobacillus*, and various fungi). Oral anaerobic bacteria (such as *Peptostreptococcus*, *Fusobacterium*, and *Bacteroides*) may be found in smaller numbers.[20]

In reality, jejunal culture fails to identify bacterial growth in one third of healthy volunteers. If organisms grow, they usually belong to the Lactobacilli or Enterococcus (positive Gram aerobic bacteria) or facultative anaerobic groups, with a concentration of up to 10^4 organisms/gram jejunal content. Colliform bacteria are often encountered in the jejunum of healthy individuals, but rarely exceed 10^3 organisms/g. Anaerobic bacteroides cannot be found in the proximal small intestines of healthy individuals.

The bacterial population in the small intestines of patients with bacterial overgrowth is highly complex and resembles that of the normal caeccum. Bacterial counts often reach 10^8-10^9 organisms/g intestinal content. Enterobacteria in the proximal intestines, including colliform bacteria, are only transient in character and few in numbers, in contrary to that in the ileum, where large numbers reside. Absolutely anaerobic bacteria, which normally cannot survive in the jejunum, often colonize the ileum.

Flora of the small intestines approaching the ileocaecal valve increases to a point similar to that of the caeccum. Removal of the ileocaecal valve increases bacterial growth. Beyond the ileocaecal valve, the number of microorganisms increases up to one million times (approximately 10^9 to 10^{12} bacteria/g colon content).[22] Flora of the large intestines are dominated by anaerobic organisms such as bacteroides, anaerobic lactobacilli, and clostridium.

Limiting Floral Growth in the Small Intestines

Several mechanisms are involved in maintaining floral balance in the intestines. The bacterial population in the jejunum, for example, is maintained at a low concentration partly by normal intestinal peristaltic contractions.[18,23,24] The gastrointestinal tract is protected from pathogenic bacteria through many ways. Acidic environment in the gaster and proteolytic enzymes secreted by gastric cells can eradicate a great number of swallowed bacteria. The contents of the small intestines and colon contain high concentrations of bile salts, toxic to several kinds of bacteria due to a detergent-like character which destroys the bacterial membrane. The parietal cells in the small intestines produce lysozymes and defensyne, which are toxic to bacteria and very effective in eliminating bacteria and viruses, and play a crucial role in inhibiting bacterial overgrowth in the small intestines.[25,26] A rapid and constant flow of the contents of the small intestines washes bacteria from the intestines. These mechanisms allow the small intestines to be relatively free from bacteria. Other factors that influence intestinal floral balance are: the tendency for bacteria to adhere to intestinal epithelial cells, epithelial factors (IgA, lysozyme, and glycoprotein), factors of the intestinal lumen (age, diet, ingested microbes, debilitation due to serious diseases, factors that influence gastrointestinal motility and antimicrobial agents).

The main factor responsible for limiting bacterial proliferation in the small intestines is the propulsive nature of the normal intestinal tract. Mucus aids this mechanical process in eliminating bacteria, supported by the fact that microorganisms tend to be concentrated in the mucus layer coating the gastrointestinal mucosa. Thus, when motility is reduced or disturbed, bacterial overgrowth quickly ensues.[27,28]

MMC works by minimizing the number of intestinal bacteria by cleansing debris and bacteria from the intestinal lumen.[29] Prolonged intestinal transit time causes bacterial overgrowth in the small intestines. The motor function of the proximal small intestines is the main determining factor of gastric emptying.[30] Inadequate propulsion of chyme from the proximal small intestines causes obstruction of gastric flow and delayed gastric emptying.[31]

THE PATHOGENESIS OF BACTERIAL OVERGROWTH

Increased bacterial flora in the lumen of the small intestines compete with the host's body in nutrient absorption, causing clinical problems due to nutrient catabolism by bacteria with toxic metabolic products and direct destruction of enterocytes.[21]

Many clinical conditions are associated with bacterial overgrowth (Table 1).[21]

Dysmotility and Bacterial Overgrowth

Abnormal bowel motility is often accompanied by reduced gastric acid secretion, which facilitates bacterial proliferation and malabsorption, such as in cases of scleroderma, bowel pseudo-obstruction, diabetic autonomous neuropathy, and liver cirrhosis.[29]

Vantrappen et al (1977) was the first researcher to

Table 1. Clinical Conditions Associated with Bacterial Overgrowth.[21]

1. Gastric proliferation :
   - Hypo or achlorhydria, particularly when accompanied by motor or anatomical disorder
   - Continuous hypochlorhydria due to proton pump inhibitor
2. Stagnation in the small intestines
   - Anatomic:
     - afferent loop from a partial Billroth II gastrectomy
     - duodeno-jejunal diverticulosis
     - surgical blind loop (end-to-end anastomosis)
     - surgicalrecirculationloop (end-to-end anastomosis)
     - obstruction (stricture, adhesion, inflammation, neoplasm)
   - Motor:
     - scleroderma
     - idiopathic intestinal pseudoobstruction
     - lack of MMC or a disturbance of MMC
     - diabetic autonomic neuropathy
   - Abnormal communication between the proximal and distal gastrointestinal tract:
     - gastro-cholic or jejuno-cholic fistule
     - ileo-caecal valve resection
   - Etc.:
     - immunodeficiency syndrome
     - chronic pancreatitis

demonstrate that absence of MMC can be an important factor in the pathogenesis of bacterial overgrowth in humans.[29] Vantrappen et al demonstrated that 5 out of 12 patients with bacterial overgrowth (based on bile acid breath test) had no MMC.

Soudah et al (1991) studied 5 patients with scleroderma and diminished MMC activity. Bacterial overgrowth was detected using the hydrogen breath test. Motility stimulation using octreotide induced MMC, clinical improvement, and excessive flora.[29]

Husebye et al (1993) studied the relationship between microflora, motility, and gastric pH in patients with symptoms of advanced radiation enteropathy. Normal MMC intensity prohibits negative Gram bacteria from growing in the duodenum. On the other hand, bacterial overgrowth in patients with disturbed MMC activity demonstrated a close correlation between the colonization of negative Gram bacteria and MMC intensity ($p < 0.001$).[29,32]

Scott and Cahall demonstrated that administration of morphine sulphate can eliminate MMC activity, thus causing significant bowel colonization by negative Gram bacteria after 6-15 hours of diminished MMC. On the other hand, stimulation of MMC activity reduces bacterial overgrowth, demonstrating that motility plays an important role in the pathogenesis of bacterial overgrowth.[29]

BACTERIAL OVERGROWTH IN LIVER CIRRHOSIS

The Clinical Aspect of Bacterial Overgrowth

Clinical manifestations of bacterial overgrowth vary, from being asymptomatic to severe diarrhea, malnutrition, and anemia, and depend on the causative small intestine abnormality.

Patients with small intestinal diverticles are relatively asymptomatic, until the population of bowel bacteria is significant enough to induce steatorrhea and increased defecation, weight loss, and anemia. Nevertheless, proliferation of microorganisms in the lumen of the small intestines create the same consequences as follows:[21,33,34,35,36,37,38,39]

- Weight loss, related to steatorrhea, in approximately one third of patients with bacterial overgrowth
- Diarrhea, due to increased water and electrolyte secretion in the colon and small intestines, due to production of bacterial secretatogue such as hydroxyl fatty acids (due to fat malabsorption) and deconjugation of bile salts (due to bile salt malabsorption).
- Fat malabsorption, due to bile acid metabolism due to the conjugation of bile salts by bacteria and destruction of bowel mucosa.
- Disturbed carbohydrate assimilation, due to bacterial fermentation, maldigestion, and malabsorption due to damaged small intestines as well as reduced disaccharide (lactase and sucrase) in erythrocytes.
- Disturbed drug metabolism, such as reduced effectiveness of L-dopa or sulphasalazine.
- Hypoproteinemia, due to reduced amino acid uptake due to damage of the mucosa of the small intestines, protein degradation and protein precursor by bacteria and enteropathy.
- Anemia (megaloblastic and macrocytic), due to cobalamine/vitamin B12 deficiency due to cobalamine uptake by bacteria.
- Hypocalcemia tetani, due to calcium malabsorption.
- Visual disturbance, due to vitamin A deficiency.
- Osteomalacia, due to vitamin D and calcium malabsorption.

The Influence of Bacterial Overgrowth on the Liver

Several complications of chronic liver disease, such as hepatic encephalopathy and spontaneous bacterial peritonitis are associated with intestinal microflora. In addition, endotoxin from intestinal bacteria has been

shown as mediator of liver damage, and reduced liver function. Hepatobilliary inflammation is associated with various clinical as well as experimental intestinal clinical disturbance, with the threat of increased permeability of the small intestines, and exposure to bowel bacteria.[40] Several studies on laboratory rats demonstrate inflammation and progressive hepatobilliary fibrosis as a response to polymerization of the cell walls of anaerobic bacteria, particularly Bacteroides sp. A part of this process is mediated by tumor necrosing factor-α (TNF α) from active Kupffer cells.

Lichtman et al (1990) in a study on laboratory rats, found progressive hepatomegally, hepatobiliary inflammation, increased plasma transmainase, and increased mortality as a result of bacterial overgrowth in the jejunum.

Shindo et al (1993) reported increased fat excretion from the feces of several patients with liver cirrhosis and bacterial overgrowth. In an experimental study in humans, it was demonstrated that bacterial overgrowth could induce hepatobilliary damage similar to that in alcoholic liver disease.

Several mechanisms explain the negative effects of bacterial overgrowth on the liver, as follows:

1. Accumulation of bacterial cell wall polymers in the liver from bacterial overgrowth in the intestines (Ledesma et al, 1996).
2. Excessive production of toxic bile acids, such as lithocolic acid, due to bacterial overgrowth (Shindo et al, 1993).
3. Increased toxic effect of alcohol due to increased capacity for ethanol metabolism, producing large amounts of acetaldehyde, which is toxic to the liver (Baraona et al, 1986).

In an experimental model on liver cirrhosis, Casafont et al found a high prevalence of bacterial translocation in animals with bacterial overgrowth associated with spontaneous bacterial peritonitis (100%) compared to those without spontaneous bacterial peritonitis (57%, $p<0.02$). Such results demonstrate that bacterial overgrowth can predispose bacterial translocation and bacterial translocation is a permissive factor for spontaneous bacterial peritonitis.[40]

The Etiology of Bacterial Overgrowth in Liver Cirrhosis

There are several possible agents that can facilitate bacterial overgrowth in patients with chronic liver disease. Several researchers think that bacterial overgrowth is not unique for chronic liver disease, since its prevalence is the same between patients hospitalized without liver disease. Thus, bacterial overgrowth may be associated with chronic disease or hospitalization. Other authors believe that bacterial overgrowth is not associated with the liver disease itself, but with its cause, such as chronic alcoholism. However, bacterial overgrowth is also found in alcoholics without liver disease. In addition, several conditions that can be found simultaneously in patients with liver cirrhosis can increase the prevalence of bacterial overgrowth.[1]

Factors that influence the development of bacterial overgrowth in patients with liver cirrhosis are as follows:

1. Intestinal dysmotility

Several studies have demonstrated changes in the motility of the proximal intestines in patients with liver cirrhosis, which delays orocecal transit time. Chesta et al (1993) found changes in the motility of the proximal intestines in patients with liver cirrhosis.[15] Cyclic activity in 14 out of 16 patients with liver cirrhosis is significantly longer (166 ± 19 minutes) compared to control (81 ± 14 minutes, $p < 0.02$). Nonetheless, dysmotility seems to not depend on the presence of bacterial overgrowth, since the bowel motility pattern in patients with liver cirrhosis with bacterial overgrowth and without bacterial overgrowth is not significantly different.

On the other hand, there is indirect evidence that supports a relationship between bacterial overgrowth and motility. Pardo et al (1997) treated a group of liver cirrhosis patients with bacterial overgrowth with prokinetic agents. They found that such treatment could facilitate small intestine transit time and produce negative jejunum culture in all but one patient.[1]

In another study, Pardo et al (2000) studied the effect of cisapride on bacterial overgrowth and bacterial translocation in liver cirrhosis.[13] They found that in laboratory animals, administration of cisapride reduced jejunum flora related with reduced bacterial translocation from the mesenteric lymph nodes. Bacterial overgrowth caused by negative Gram bacteria is relatively more often in patients with liver cirrhosis and cisapride, and could facilitate the elimination of bacterial overgrowth. Such results demonstrated that prokinetic agents could be beneficial in preventing bacterial translocation in patients with liver cirrhosis, and also support other controlled studies in determining the benefit of prokinetic agents as an adjuvant or alternative treatment for selective decontamination with antibiotics, aimed as a prophylaxis for enteric-originated infection in liver cirrhosis.

Van Thiel et al (1994) evaluated the effect of grade 0 and 1 chronic hepatic encephalopathy on gastric emp-

tying and orocecal transit time.[4] The results demonstrated that chronic hepatic encephalopathy is related to elongated orocecal transit time that is not caused by delayed gastric emptying, and that treatment of chronic hepatic encephalopathy with antibiotics and protein restriction can reduce orocecal transit time.

2. Achlorhydria

Gastric secretion has been known to be one of the most important defense mechanisms for bacterial overgrowth. Even though the results are inconsistent, several studies have demonstrated low gastric acid secretion in patients with liver cirrhosis (Fraser et al, 1993, and Gaur et al 1988). Thus, it is not surprising if several studies found a correlation between bacterial overgrowth and gastric hypoacidity in patients with liver cirrhosis. Bode et al (1984) discovered that the number of microorganisms in the jejunum fluid has a close correlation with the pH level of gastric acid, while Shindo et al (1993) found a close correlation with $^{14}CO_2$ activity and gastric pH.[1]

3. Local immunodeficiency

Intestinal IgA deficiency is said to cause exacerbation of bacterial overgrowth. While it is known that there is reduced bowel IgA production in alcoholic liver cirrhosis (Pelletier et al, 1982), which is another possible mechanism that supports bacterial overgrowth in patients with liver cirrhosis.[1]

4. Malnutrition

Malnutrition has been known to be a cause of bacterial overgrowth, and is often found in patients with liver cirrhosis (Ledesma et al, 1996). Casafont et al (1995) found a tendency for patients with liver cirrhosis and bacterial overgrowth to be in a worse nutritional state compared to those without bacterial overgrowth, even though the difference was not significantly different.[1]

5. Bile acid

Bile acid influences the symbiotic relationship between bowel bacteria and the host. In reality, bile acid can inhibit bacterial growth with its bacteriostatic nature, and/or inhibit bacterial adhesion with its detergent-like nature.[42] Several studies have demonstrated that bile duct ligation causes bacterial invasion and translocation to lymph nodes (Kalambaheti et al, 1994, and Chuang et al, 1997). Increased bacterial colonization in the small intestines has also been reported in patients with liver cirrhosis, where bile acid secretion into the intestines is reduced (Morencos et al, 1995).[42]

Many studies on bacterial overgrowth in patients with chronic liver disease and liver cirrhosis have been conducted (Table 2). Martini et al (1956) demonstrated the contamination of the proximal small intestines in 75% of patients with liver cirrhosis. The microorganisms found in the duodenum and jejunum are colliform and enterococcus. Lal et al (1972) studied the microflora of the small intestines of patients with alcoholic liver cirrhosis by conducting intestinal aspiration fluid culture and demonstrated abnormal colonization in the proximal small intestines of 12 out of 24 patients (50%). Shindo et al (1993) found 27% with bacterial overgrowth in groups of patients with liver cirrhosis. The bacteria found were mostly species capable of deconjugating bile salts.[1]

Bode et al (1993) in another study on hydrogen breath test to evaluate the incidence of bacterial overgrowth in 45 chronic alcoholics, found more bacterial overgrowth (37.8%) compared to control groups (13.3%). Even though bacterial overgrowth is more commonly found in patients with liver cirrhosis (42.9%) compared to those without liver cirrhosis (33.3%), the difference was not found to be statistically significant.

Chesta et al (1991) found bacterial overgrowth in 45% of patients with liver cirrhosis using the lactulose breath test and 64% of patients with liver cirrhosis using jejunum culture. In this study, bacterial overgrowth is associated with the degree of liver disease, not the cause of liver cirrhosis, since its prevalence in patients with alcoholic liver disease and non-alcoholic liver disease is the same.

Casafont et al (1995) studien 89 patients with alcoholic liver cirrhosis using the glucose hydrogen breath test, and found bacterial overgrowth in 30.3% of patients. Bacterial overgrowth in this study was not associated with the activity of liver disease or regular alcohol consumption during the study. However, there was a correlation between bacterial overgrowth and the degree of liver cirrhosis. A higher prevalence was found in patients classified into Child-Pugh class C (48.3%) compared to class B (27%), and class A (13.1%, $p < 0.02$). In addition, bacterial overgrowth was greater in patients with ascites (37.1%) compared to those without ascites (5.3%, $p < 0.02$).[1]

Pardo et al (200) in a study, studied the effect of cisapride on bacterial overgrowth and bacterial translocation in liver cirrhosis and found the prevalence of bacterial overgrowth to be 50% (23 out of 46 patients with liver cirrhosis), and even though the difference was not statistically significant, the bacterial overgrowth of patients with ascites and active alcoholism is greater than in those without (78% compared to 56%, and 74% compared to 52%).[13]

DIAGNOSTIC TEST FOR BACTERIAL OVERGROWTH

There are three approaches that may be used to evaluate bacterial overgrowth, which are aspiration fluid culture, indirect evaluation, and monitoring treatment with antibiotics (Table 3).[18]

Table 2. The Prevalence of Bacterial Overgrowth in the Intestines in Chronic Liver Disease and Liver Cirrhosis

Researcher (year)	Subject	Diagnostic test	Result
Martini et al (1956)	Liver cirrhosis	Culture	75%
Lai et al (1972)	Alcoholic liver cirrhosis	Culture	50%
Chesta et al (1991)	Alcoholic and non-alcoholic liver cirrhosis	Culture/hydrogen breath test	64% / 45%
Shindo et al (1993)	Liver cirrhosis	Culture	27%
Bode et al (1993)	Chronic alcoholism	hydrogen breath test	37.8%
Casafont et al (1995)	Alcoholic liver cirrhosis	hydrogen breath test	30.3%
Pardo et al (2000)	Liver cirrhosis	Culture	50%

Table 3. Diagnostic Test for Bacterial Overgrowth in the Intestines[18]

- Indirect measurement of bacterial metabolism effects:
  - Circulation:
    Free bile acids
  - Urine:
    Amino acid derivatives
    Indol (from triplophane)
    Fenol (from tyrosine)
    Hypuric acid (from fenitalanine)
    Piperidin (from lysine)
    Pirolidin (from arginine and ornithine)
  - Exhalation:
    CO_2 from: bile acids, labeled with ^{14}C (glycholic acid)
    Carbohydrates, labeled with ^{14}C (xylose)
    Amino acids, labeled with ^{14}C (taurine)
    Hydrogen from: absorbed sugars (glucose)
    Unabsorbed sugars (lactulose)
- Direct measurement of bacteria and metabolites:
  Life bacterial count
  Volatile fatty acid concentration
  Presence of deconjugated bile acids
- Response to therapy:
  Improvement of clinical indications of malabsorption (such as fat, vitamin B12, and xylose)

The gold standard evaluation of bacterial overgrowth is culture of aspiration fluid from the proximal small intestines.[18,28] However, the technique is very complicated. Samples have to be taken with care and culture of aspiration fluid from the proximal small intestines must be conducted correctly. Samples must be taken in anaerobic conditions, must be diluted repeatedly, and cultured in several selective (aerobic and anaerobic) media. There is also the possibility of missing the spots of bacterial overgrowth, if only a single culture is performed, since bacterial overgrowth may only be found in the distal portion of the small intestines. Intestinal intubation is performed by means of endoscopy, preferably using a double lumen, which is quite expensive and is only conducted by experts in gastroenterology. Sampling also has the risk of contamination. Microbiologic analysis also requires large amounts of time and money.[21] Thus, several diagnostic tests have been conducted to replace jejunum aspiration fluid culture (Table 4).[21]

MANAGEMENT OF BACTERIAL OVERGROWTH

In general, it is important to know the underlying disease in bacterial overgrowth and the gastrointestinal symptoms or nutritional deficiency that occurs, since the management approach depend on the cause and the predisposing factors. Ideally, the cause should be eliminated and the predisposing factors modified. However, this is rarely possible.[18] Patients with anatomic abnormality can generally be cured through the appropriate gastrointestinal surgery, while most patients produce satisfactory outcome with conservative treatment alone. Malnutrition is also a predisposing factor for bacterial overgrowth. Thus, correction of nutritional deficiency or nutritional support is crucial for the healing process.

Table 4. Diagnostic Test for Bacterial Overgrowth.[21]

Diagnostic test	Practicality	Sensitivity	Specificity	Security
Culture	Unsatisfactory	Excellent	Excellent	Good
Urine indicant	Good	Unsatisfactory	Unsatisfactory	Excellent
Jejunum fatty acid	Unsatisfactory	Satisfactory	Excellent	Good
Jejunum bile acid	Unsatisfactory	Satisfactory	Excellent	Good
Fasting H2 breath test	Excellent	Unsatisfactory	Good	Excellent
^{14}C Bile acid breath test	Excellent	Satisfactory	Unsatisfactory	Good
^{14}C Xylose breath test	Excellent	Excellent	Excellent	Good
H2-lactulose breath test	Excellent	Satisfactory	Satisfactory-Good	Excellent
H2-glucose breath test	Excellent	Good	Satisfactory-Good	Excellent

The strategy to reduce intestinal bacteria and bacterial translocation in patients with liver cirrhosis and in laboratory animals mostly incorporates selective intestinal decontamination. In addition, it has been known that excessive activity of the sympathetic system is a classic finding in liver cirrhosis with ascites, and that sympathetic stimulation can delay intestinal transit time. This can be prevented by inhibiting β-adrenoseptor (McIntyre et al, 1992, and Ahluwalia et al, 1994). Beta inhibitor reduces portal pressure, which improves bowel defense in liver cirrhosis, thus reducing the incidence of bacterial translocation.[12]

Perez-Paramo et al (2000) conducted a study on

laboratory animals to study the effect of propranolol on intestinal bacteria, bowel transit time, intestinal permeability, and the incidence of bacterial translocation. Compared to placebo groups, animals treated with propranolol significantly had lower portal pressure, a shorter bowel transit time, and lower incidence rates for bacterial overgrowth and bacterial translocation. In this case, bacterial translocation is associated with intestinal hypomotility. Propranolol reduces bowel transit time, reduces the incidence of bacterial overgrowth and bacterial translocation.[12]

Patients with bacterial overgrowth or diseases that predispose bacterial overgrowth should be cautious and avoid drugs that disturb bowel motility, such as anticholinergics, antidepressants, neuroleptics, analgesics, and sedatives.[29] In addition, normal gastric acid secretion is important in such patients. Thus, gastric acid secretion inhibitors should be administered with caution.[29]

Administration of prokinetic agents such as cisapride may be given at a dose of 3 times 10 mg daily.[29] Pardo et al (2000) conducted a study on patients with liver cirrhosis and laboratory animals using 20 mg of cisapride twice daily for one week.[13] Following treatment, the orocecal transit time was significantly reduced, followed by elimination of bacterial overgrowth in 4 out of 5 patients treated, while bacterial overgrowth persisted in untreated patients. In laboratory animals, administration of cisapride reduced jejunum flora, accompanied by significant reduction of bacterial translocation to the mesenteric lymph nodes.

CONCLUSION

- Bacterial overgrowth in the small intestines refer to all conditions where the proximal portion of the small intestines contain over 10^5 organism/ml intestinal fluid for prolonged periods of time.
- In liver cirrhosis, factors that predispose bacterial overgrowth are associated with bowel dysmotility, achlorhydria, local immunodeficiency, malnutrition, and low levels of bile acid.
- Clinical manifestations of bacterial overgrowth in liver cirrhosis is associated with hepatobiliary damage, increased levels of endotoxin, increased toxic bile acids, increased toxic effect of alcohol, and increased incidence of spontaneous bacterial peritonitis.
- The hydrogen breath test is a non-invasive, safe, quick, easy, and relatively cheap diagnostic method for bacterial overgrowth. It is recommended for clinical use.
- Treatment of bacterial overgrowth in liver cirrhosis should take into consideration predisposing factors and nutritional support, avoidance of drugs that reduce bowel motility and gastric acid secretion, as well as the use of propranolol and prokinetic agents.

REFERENCES

1. Casafont F, Martin L, Pons-Romero F. Bacterial overgrowth in the small intestine in chronic liver disease. In: Blum HE, Bode Ch, Bode JCh, Sartor RB editors. Gut and the liver 1st ed. Dordrecht: Kluwer Academic Publishers: 1998. p.332–7.
2. King CE, Toskes PP. Bacterial overgrowth syndromes. In: Berk JE editor. Bockus gastroenterology. 4th ed. Philadelphia: WB Saunders Company; 1985. 1781–91.
3. Bouhnik Y, Alain S, Attar A, Flourie B, Raskine L, Sanson-LePors MJ, et al. Bacterial populations contaminating the upper gut in patients with small intestinal bacterial overgrowth syndrome. Am J Gastroenterol 1999;94:1327–31.
4. Davidson GP, Robb TA, Kirubakaran CP. Bacterial contamination of the small intestine as an important cause of chronic diarrhea and abdominal pain: Diagnosis by breath hydrogen test. Pediatrics 1984;74:229–35.
5. Lichtman SN, Keku J, Schwab JH, Sartor RB. Hepatic injury associated with small bowel bacterial overgrowth in rats is prevented by metronidazole and tetracycline. Gastroenterology 1991;100:513–9.
6. Thurman RG, Bradford BU, Iimura Y, Knecht KT, Arteel GE, Yin M, et al. The role of gut-derived bacterial toxins and free radicals in alcohol-induced liver injury. J Gastroenterol Hepatol 1998;13 Suppl:S39–50.
7. Adachi Y, Moore LE, Bradford BU, Gao W, Thurman RG. Antibiotics prevent liver injury in rats following long-term exposure to ethanol. Gastroenterol 1995;108:218–24.
8. Banwell JG, Kistler LA, Giannella RA, Weber FL, Lieber A, Powell DE. Small intestinal bacterial overgrowth syndrome. Gastroenterol 1981;80:834–45.
9. Berg RD. Bacterial translocation. In: Blum HE, Bode Ch, Bode JCh, Sartor RB editors. Gut and the liver. 1st ed. Dordrecht: Kluwer Academic Publishers: 1998. p.47–60.
10. Ochs A. Spontaneous bacterial peritonitis: Incidence, diagnosis and clinical course. In: Blum HE, Bode Ch, Bode JCh, Sartor RB editors. Gut and the liver. 1st ed. Dordrecht: Kluwer Academic Publishers: 1998. p.341–53.
11. Guarner C, Runyon BA, Young S, Heck M, Sheikh Y. Intestinal bacterial overgrowth and bacterial translocation in cirrhotic rats with ascites. J Hepatol 1997;26:1372–8.
12. Perez-Paramo M, Munos J, Albillos A, Freile I, Portero F, Santos M, et al. Effect of propranolol on the factors promoting bacterial translocation in cirrhotic rats with ascites. Hepatol 2000;31:43–8.
13. Pardo A, Bartoli R, Lorenzo-Zuniga V, Planas R, Vinado B, Riba J, et al. Effect of cisapride on intestinal bacterial overgrowth and bacterial translocation in cirrhosis. Hepatol 2000;31:858–63.
14. Garcia-Tsao G, Lee FY, Barden GE, Cartun R, West AB. Bacterial translocation to mesenteric lymph nodes is increased in cirrhotic rats with ascites. Gastroenterol 1995;108:1835–41.
15. Chesta J, Defilippi C, Defilippi C. Abnormalities in proximal small bowel motility in patients with cirrhosis. Hepatol 1993;17:828–32.
16. Sorell WT, Quigley EMM, Jin GL, Johnson TJ, Rikkers LF.

Bacterial translocation in the portal-hypertensive rat: Studies in basal conditions and on exposure to hemorrhagic shock. Gastroenterol 1993;104:1722–6.
17. Casafont F, Sanchez E, Martin L, Aguero J, Pons-Romero F. Influence of malnutrition on the prevalence of bacterial translocation and spontaneous bacterial peritonitis in experimental cirrhosis in rats. Hepatol 1997;25:1334–7.
18. Ghosh P, Neale G. Bacteriology of the small gut and bacterial overgrowth. In: Bouchier IAD, Allan RN, Hodgson HJF, Keighley MRB editors. Gastroenterology: Clinical science and practice. 2nd ed. London: WB Saunders Company Ltd.; 1993. p.499–522.
19. Volk WA, Gebhardt BM, Hammarskjold ML, Kadner RJ. Essentials of medical microbiology. 5th ed. Philadelphia: Lippincot Raven Publishers; 1996. p.315–28.
20. Simon GL, Gorbach SL. Intestinal flora in health and disease. Gastroenterol 1984;86:174–93.
21. Toskes PP, Donaldson RM Jr. Enteric bacterial flora and bacterial overgrowth syndrome. In: Sleisenger MH, Fordtran JS, Scharschmidt BE, Feldman M editors. Gastrointestinal disease: Pathophysiology/diagnosis/management. 5th ed. Philadelphia: WB Saunders Company; 1993. p.1106–18.
22. Jr RB Drude, Jr C Hines. The pathophysiology of intestinal bacterial overgrowth syndromes. Arch Intern Med 1980;140:1349–52.
23. Adinolfi MF, Cerise EJ, Nichols RL. Microbiology of the small intestine. In: Nelson RL, Nyhus LM editors. Surgery of the small intestine. 1st ed. Norwalk: Appleton & Lange; 1987. p.39–46.
24. Muscroft TJ, Deane SA, Youngs D, Burdon DW, Keighley MRB. The microflora of the postoperative stomach. Br J Surg 1981;68:560–4.
25. Salyers AA, Whitt DD. Bacterial pathogenesis: a molecular approach. 1st ed. Washington DC: ASM Press; 1994. p.11–3.
26. Van Beers EH, Buller HA, Grand RJ, Einerhand AWC, Dekker J. Intestinal brush border glycohydrolases: Structure, function, and development. Crit Rev Biochem Mol Biol 1995;30:197–262.
27. Rani AA, Gangguan motilitas SCBA. In: Manan C, Djojoningrat D, Simadibrata M. Naskah lengkap simposium motilitas saluran cerna & nutrisi. Jakarta: Pendidikan Berkesinambungan Bagian Ilmu Penyakit Dalam Fakultas Kedokteran Universitas Indonesia; 1994. p.29–36.
28. Santangelo WC, Krejs GJ. Diarrhea of small intestinal origin. In: Nelson RL, Nyhus LM editors. Surgery of the small intestine 1st ed. Norwalk: Appleton& Lange; 1987. p.47–58.
29. Husebye E. Gastrointestinal motility disorders and bacterial overgrowth. J Intern Med 1995;237:419–27.
30. Camilleri M. Motility disorders of the intestine. In: Bouchier IAD, Allan RN, Hodgson HJF, Keighley MRB editors. Gastroenterology: clinical science and practice 2nd ed. London: WB Saunders Company Ltd.; 1993. p.483–98.
31. Akkermans LMA. The history and development of motility research in the 20th century. Motility 1997;40:4–8.
32. Husebye E, Hellstrom PM, Midtvedt T. Intestinal microflora stimulates myoelectric activity of rat small intestine by promoting cyclic initiation and aboral propagation of migrating myoelectric complex. Dig Dis Sci 1994;39:946–56.
33. Thea DM, Keusch G. Digestive system. In: Schaechter M, Medoff G, Schlessinger D editors. Mechanisms of microbial disease. 1st ed. Baltimore: Williams & Wilkins; 1989. p.628–50.
34. Giannella RA, Broitman SA, Zamcheck N. Competition between bacteria and intrinsic factor for vitamin B_{12}: Implications for vitamin B_{12} malabsorption in intestinal bacterial overgrowth. Gastroenterol 1972;62:255–60.
35. King CE, Toskes PP. Protein-losing enteropathy in the human and experimental rat blind-loop syndrome. Gastroenterol 1981;80:504–9.
36. Donowitz M, Kokke FT, Saidi R. Evaluation of patients with chronic diarrhea. N Engl J Med 1995;332:725–9.
37. Ament ME, Shimoda SS, Saunders DR, Rubin CE. Pathogenesis of steatorrhea in three cases of small intestinal stasis syndrome. Gastroenterol 1972;63:728–47.
38. Batt RM, McLean L. Comparison of the biochemical changes in the jejunal mucosa of dogs with aerobic and anaerobic bacterial overgrowth. Gastroenterol 1987;93:986–93.
39. Bauer TM. The role of gut bacteria in drug metabolism. In: Blum HE, Bode Ch, Bode JCh, Sartor RB editors. Gut and the liver. 1st ed. Dordrecht: Kluwer Academic Publishers; 1998. p.177–81.
40. Sartor RB, Lichtman SN. Hepatic injury and biliary tract diseases associated with small intestinal bacterial overgrowth. In: Blum HE, Bode Ch, Bode JCh, Sartor RB. Gut and the liver. Dordrecht: Kluwer Academic Publishers; 1998. p.241–50.
41. Van Thiel DH, Fagiuoli S, Wright III, Chien MC, Gavaler JS. Gastrointestinal transit in cirrhotic patients: Effect of hepatic encephalopathy and its treatment. Hepatol 1994;19:67–71.
42. Hofmann AF, Hagey LR. Bile acids and intestinal bacteria: Peaceful coexistence versus deadly warfare. In: Blum HE, Bode Ch, Bode JCh, Sartor RB, editors. Gut and the liver. 1st ed. Dordrecht: Kluwer Academic Publishers; 1998. p.85–103.